Characteristics Influencing the Effective Administration of Drugs as Inhalation Aerosols

Studies of the effective delivery of pharmaceutical inhalation aerosols have hinged on their particle-size characteristics and the mass, or dose, of drug delivered to the lung. Preparation and delivery of aerosols have been approached using these criteria with the intention of optimizing lung deposition.

Aerosol particles and droplets exhibit a range of sizes which constitute their distribution. The best statistical fit to this distribution is frequently log-normal. The expressions used to define particle-size distributions are the mass median aerodynamic diameter and the geometric standard deviation. The general characteristics of an aerosol that result in appropriate lung deposition and therapeutic effect have been known for some time. Particles with a median diameter up to 5 μm will be deposited predominantly in the lungs. Such particles are considered respirable, and the term “respirable fraction” has been used to describe the proportion of the total distribution in this approximate size range. A narrow distribution will result in higher deposition in the periphery, while a broad distribution will result in increased central and upper airway deposition.

The development of pressurized metered dose inhalers (MDIs) for the administration of aerosols was a major advance in drug therapy. The efficiency of these devices has been subject to scrutiny. Despite their delivery of a therapeutically effective dose, this constitutes a small proportion of the total dose delivered by the device. Efforts have been directed to increase efficiency or eliminate redundancy of the devices. Particles generated by an MDI are most significantly influenced by inertial and sedimentary mechanisms of deposition. These are subject to kinetic factors related to velocity and evaporation of droplets following generation. The distance and direction traveled by each of the droplets prior to entry into the lung will influence the particle-size distribution and the dose delivered. It has been shown that deposition in the oropharynx may be reduced by administering aerosols through spacer devices. When aerosols are delivered by other methods, the influence of the administration accessories upon particle size and dose delivery must be considered.

The issue of delivery of aerosols to mechanically ventilated patients has been considered. Aerosols are administered via endotracheal tubing for this purpose.

In this issue of Chest, Taylor et al (see page 920) have considered the effect of using intraluminal catheters (ILCs) to deliver aerosols through endotracheal tubes. They have studied the effect of ILCs as a function of diameter and length upon the delivery of salbutamol (albuterol) delivered by MDI (Ventolin, 100 μg per puff). Their method involves the in vitro assessment of aerosols exiting a tracheal tube when ILCs of known length and diameter are employed. The authors conclude that the ILCs act as an extension of the actuator nozzle. Thus, a larger respirable fraction of aerosol reaches the end of the tracheal tube through long, narrow ILCs. Optimal dosing, logically, occurs when the catheter extends the full length of the tracheal tube.

This is a unique approach to overcoming the problems of deposition of aerosols in the upper respiratory tract or in administration accessories during administration to mechanically ventilated patients. The authors have satisfied the usual criteria for assessment of the efficiency of their system by considering particle size and dose delivery.

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Bacteremic Pneumococcal Pneumonia Mortality Rate
Is It Really Different in Sweden?

Austrian and Gold\(^1\) in 1964 published the results of their observations of 2,000 episodes of community-acquired pneumonia studied in New York City between 1952 and 1962. Of the 2,000 patients, 529 (26.5 percent) were bacteremic with *Streptococcus pneumoniae*. The mortality rate for the bacteremic patients was 19.5 percent. These investigators noted that 43 percent of the deaths (36 percent in those receiving treatment) occurred within 24 h of admission.

This observation has been confirmed repeatedly over the past three decades.\(^2,3\) Norrby and Pope,\(^4\) in a review of pneumococcal pneumonia, presented the mortality rates reported as part of studies of pneumococcal bacteremia. Seven of these studies were from the United States, where the mortality rates ranged from 15 to 35 percent. There were two studies from the United Kingdom with mortality rates of 25 and 50 percent (the latter study had only 32 patients); two small studies (n = 19 and n = 25) from France with mortality rates of 28 and 48 percent; and one study from Finland of 110 patients with a mortality rate of 15 percent. In the study from Israel by Kramer et al.,\(^5\) the mortality rate among adults was 33 percent. Indeed, the mortality rate of bacteremic pneumococcal pneumonia (BPP) has not been reduced despite major advances in intensive care medicine.\(^6\)

In this issue of *Chest* (see page 710), Örtqvist et al report that the mortality rate from bacteremic pneumococcal pneumonia was 5 percent in Stockholm, while it was 26 percent in Huntington, West Virginia. Why is there such a difference? Is the mortality rate from BPP really lower in Sweden, and if so, why is it lower?

The first question—why is there such a difference in the mortality rate from BPP between Stockholm and Huntington?—cannot be answered from the Örtqvist article. The two studies were carried out independently over roughly the same time periods (1977-1984 for the Swedish study and 1978-1988 for the West Virginia study), and then the investigators 3 years later redefined their study populations so that they could carry out a comparison. Data collection instruments were apparently identical.

The mean age of the Swedish patients was lower than that of the West Virginia patients; however, the mortality rate was significantly lower in Sweden for all age groups when patients were stratified into three age groups (18 to 44, 45 to 64, and 65 years and older). While alcoholism was much more common in Sweden, the mortality rate among alcoholics was similar in the two cities. Nevertheless, alcoholics accounted for 63 percent (7 of 11) of all deaths in the Swedish cohort. Preexisting chronic diseases were more common in West Virginia than in Sweden, and more deaths occurred among patients with chronic cardiac disease in West Virginia patients (20/49 [41 percent] vs 2/80 [3 percent]) than in Sweden. This suggests that the definitions of heart disease may have been very different in the two studies and/or that the severity of the heart disease was different. Grading functional cardiac disability according to the New York Heart Association classification would have allowed for comparison of mortality according to the class of functional disability. Incorporation of a severity of illness scoring system (better still, a pneumonia-specific one) into a prospective study of this type is necessary before we can conclude that there truly is a difference in mortality between Swedes with BPP and Americans with the same illness.

Changes in the epidemiology of pneumococcal bacteremia and BPP are occurring. In some areas, pneumococcal bacteremia is now more common in women than in men. Bruyn et al.,\(^7\) in a study of 147 episodes of pneumococcal bacteremia carried out in Leiden, The Netherlands, from 1976 to 1986, noted that women outnumbered men 1.46:1. In our study\(^8\) in Halifax, we found that women outnumbered men 1.35:1. The rate of pneumococcal bacteremia among 754 patients with community-acquired pneumonia who did not receive antibiotics prior to admission was 4.7 percent, compared with 26.4 percent in the study conducted by Austrian and Gold\(^9\) in the 1950s and 1960s. The overall rate of pneumococcal bacteremia, however, seems to be increasing; the rate in Charleston County, South Carolina, increased 2.3-fold from 1974-1976 to 18.7/100,000 in 1986-1987.\(^8\)

There has been a change in the frequency with which particular *S pneumoniae* capsular polysaccharides are isolated. Types 1, 2, and 3 accounted for more than 50 percent of cases of lobar pneumonia in the 1930s and 1940s; now serotypes 14,4,1,6A/6B; 3,8,7F; 23F; and 18C are the most frequent causes of pneumococcal disease.\(^9\) While geographic differences in the distribution of the various pneumococcal serotypes are well established, this was not a factor in the present study.

The virulence factors common to all pneumococci are capsular polysaccharides, C polysaccharide, pneumolysin, neuraminidase, pneumococcal surface pro-